Effect of Menopausal Status on Insulin-Stimulated Glucose Disposal

Comparison of middle-aged premenopausal and early postmenopausal women

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OBJECTIVE — Studies in animal models suggest that ovarian hormone deficiency is associated with the development of insulin resistance. In women, ovarian hormone levels are dramatically reduced after the menopause transition. However, the effect of the menopause transition on insulin sensitivity is unclear. Thus, we examined the effect of menopausal status on insulin sensitivity.

RESEARCH DESIGN AND METHODS — Insulin-stimulated glucose disposal was measured in 43 middle-aged premenopausal women (47 ± 3 years of age) during the luteal phase of the menstrual cycle and 40 early postmenopausal women (51 ± 4 years; time since menopause, 21 ± 13 months) using the hyperinsulinemic-euglycemic clamp technique. Body composition was measured by dual-energy X-ray absorptiometry and abdominal fat distribution by computed tomography.

RESULTS — No difference in fat-free mass (FFM) was found between groups. Total body ($P < 0.01$), subcutaneous abdominal ($P < 0.05$), and intra-abdominal ($P < 0.01$) adiposity were greater in postmenopausal women compared with premenopausal women. No differences in insulin-stimulated glucose disposal were found between premenopausal and postmenopausal women on an absolute basis (pre, 436 ± 130 vs. post, 446 ± 120 mg/min), when expressed relative to FFM (pre, 10.7 ± 3.0 vs. post, 11.5 ± 3.6 mg · kg^{-1} FFM · min^{-1}) or when statistically adjusted for FFM (pre, 436 ± 125 vs. post, 445 ± 126 mg/min).

CONCLUSIONS — These results suggest that menopausal status does not affect insulin sensitivity, as measured by the hyperinsulinemic-euglycemic clamp technique.

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In humans, the menopause transition marks the cessation of ovarian function and dramatic reductions in circulating estrogen and progesterone concentrations (1). Both estrogen and progesterone have been shown to influence insulin sensitivity (2–5). A preliminary longitudinal study from our laboratory found an increase in fasting insulin levels in women as they traverse from the premenopausal to postmenopausal state, suggesting reduced insulin sensitivity with ovarian hormone deficiency. More detailed evidence for an effect of ovarian hormones on insulin sensitivity is provided by animal studies, which show that ovariectomy reduces whole-body insulin-stimulated glucose disposal (4,5). In rats, Kumagai et al. (4) found that an ovariectomy decreased insulin-stimulated glucose disposal by decreasing skeletal muscle glucose uptake and glycogen synthesis. Similarly, Puah and Bailey (3) found that an ovariectomy decreased insulin-stimulated skeletal muscle glucose uptake in mice. Finally, Rincon et al. (5) showed that ovariectomized rats exhibited decreased insulin-stimulated glucose disposal and reduced skeletal muscle glycogen synthase expression. Taken together, these results suggest that ovarian hormone deficiency is associated with decreased insulin-stimulated glucose uptake. Moreover, ovarian hormones may influence glucose uptake by regulating nonoxidative glucose disposal in skeletal muscle. These preliminary studies support the notion that postmenopausal status might be associated with reduced insulin sensitivity.

Contrary to this hypothesis, however, the 1 study that measured insulin sensitivity in pre- and postmenopausal women found a 50% greater insulin sensitivity in postmenopausal women (6). Therefore, the effect of ovarian hormone deficiency on glucose metabolism remains unclear and understudied. To address this question, we measured whole-body insulin-stimulated glucose disposal in healthy middle-aged premenopausal and early postmenopausal women using the hyperinsulinemic-euglycemic clamp technique. Based on animal studies (3–5) and our previous longitudinal work (2), we hypothesized that insulin-stimulated glucose disposal would be lower in postmenopausal compared with premenopausal women.

RESEARCH DESIGN AND METHODS

Subjects

Volunteers were recruited from 2 ongoing studies from Burlington, Vermont, and surrounding areas through advertisements in local newspapers. Premenopausal volunteers were recruited to participate in the Vermont Longitudinal Study of the Menopause, a 5-year study examining changes in energy expenditure, body composition, abdominal fat distribution, and metabolic function in

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Abbreviations: CT, computed tomography; FFM, fat-free mass; GCRC, General Clinical Research Center.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

women as they traverse menopause. Data from the first-year evaluation are presented. Data from this cohort have been published previously, examining correlates of energy expenditure, substrate oxidation, and cardiovascular disease risk (7,8). Moreover, we have reported differences in body composition and fat distribution between premenopausal women and a subsample of postmenopausal women (9). Postmenopausal women were recruited to participate in a study examining the effect of hormone-replacement therapy on glucose homeostasis and abdominal fat distribution. Baseline pretreatment data from this study are presented. Data from postmenopausal volunteers have been published, examining correlates of insulin sensitivity (10).

The inclusion criteria for premenopausal women were as follows: *1*) between 40 and 52 years of age; *2*) premenopausal, as defined by the occurrence of 2 menses in the 3 months preceding testing, no increase in cycle irregularity in the 12 months preceding testing, and a follicle-stimulating hormone level <30 IU/l; *3*) nonsmoking; *4*) normal electrocardiogram at rest and during an exercise test; *5*) weight stability (± 2 kg) during the 6 months before testing; and *6*) BMI ≤30 kg/m^2. Premenopausal women were excluded if they *1*) were or planned on becoming pregnant; *2*) had a history or current diagnosis of diabetes, heart disease, hypertension, or other chronic disease; *3*) were taking hormone-replacement therapy, oral contraceptives, chronic steroid therapy, neuroleptics, or other medication that could affect insulin sensitivity; *4*) had a history of alcohol or drug abuse; or *5*) were glucose intolerant, defined as a fasting glucose level of ≥6.22 mmol/lor a 2-h glucose level of >7.77 mmol/l after a 75-g oral glucose load.

The inclusion criteria for postmenopausal women were as follows: *1*) early postmenopausal, as defined by the absence of menses for at least 6 months but not >5 years and a follicle-stimulating hormone level >30 IU/l, and *2*) BMI ≤30 kg/m^2. The exclusion criteria for postmenopausal women were identical to premenopausal women except that glucose intolerance was defined as a fasting glucose level >6.22 mmol/l.

The nature, purpose, and possible risks of each study were explained to each subject before she gave written consent to participate. The experimental protocols were approved by the Committee on Human Research at the University of Vermont.

Experimental protocol

Each prospective volunteer underwent an outpatient screening visit at which time medical history, physical examination, biochemical laboratory tests, treadmill test (premenopausal women only), and an oral glucose tolerance test (premenopausal women only) were performed. Volunteers who met the eligibility criteria after screening and consented to participate were studied during inpatient visits to the General Clinical Research Center (GCRC). For 3 days before inpatient visits, all subjects consumed a standardized weight-maintenance diet provided by the Metabolic Kitchen of the GCRC (60% carbohydrate, 25% fat, and 15% protein). Premenopausal women underwent 2 inpatient visits. The first inpatient visit occurred during the follicular phase of the menstrual cycle and the second inpatient visit during the luteal phase. Computed tomography scans were performed the evening of admission of the first inpatient visit and dual-energy X-ray absorptiometry the following morning. The second inpatient visit occurred 10 days after the first visit. Insulin sensitivity was measured the morning of the second inpatient visit. Postmenopausal women underwent 1 inpatient visit. Computed tomography scans were performed the evening of admission. The next morning, insulin sensitivity was measured followed by dual-energy X-ray absorptiometry measurements.

Hyperinsulinemic-euglycemic clamp

A 2-h hyperinsulinemic-euglycemic clamp was performed according to the method of DeFronzo et al. (11). Briefly, insulin was infused at 40 mU · m^{-2} · min^{-1} to approximate postprandial insulin levels. Euglycemia was maintained by a variable rate infusion of 20% dextrose. The plasma glucose level was monitored every 5 min and the dextrose infusion rate adjusted to maintain euglycemia. The average glucose infusion rate (mg/min) from 90 to 120 min was calculated as a proxy measure of insulin sensitivity (i.e., insulin-stimulated glucose disposal).

Computed tomography

Intra-abdominal and abdominal subcutaneous adipose tissue areas were measured by computed tomography (CT) with a GE High Speed Advantage CT scanner (General Electric Medical Systems, Milwaukee, WI), as described (8). Subjects were examined in the supine position with both arms stretched above the head. The scan was performed at the L4-L5 vertebrae level using a scout image of the body to establish the precise scanning position. Intra-abdominal adipose tissue area was quantified by delineating the intra-abdominal cavity at the internalmost aspect of the abdominal and oblique muscle walls and the posterior aspect of the vertebral body. Adipose tissue was highlighted and computed using an attenuation range from −190 to −30 Hounsfield U. The subcutaneous adipose tissue area was quantified by highlighting adipose tissue located between the skin and the externalmost aspect of the abdominal muscle wall.

Body composition

Fat mass, fat-free mass (FFM), and bone mineral mass were measured by dual-energy X-ray absorptiometry using a Lunar DPX-L densitometer (Lunar, Madison, WI). All scans were analyzed using the Lunar Version 1.3y DPX-L extended-analysis program for body composition.

Hormone and substrate measurements

Glucose was measured by the glucose oxidase method using an automated analyzer (YSI, Yellow Springs, OH). Serum insulin was determined by a double-antibody radioimmunoassay (Diagnostic Products, Los Angeles, CA). The intra- and interassay coefficients of variation for insulin were 4 and 10%, respectively.

Statistics

Differences between variables were determined by the unpaired Student's *t* test. Analysis of covariance was used to examine differences between groups after statistically removing the effect of selected covariates. In addition to statistical adjustment, insulin sensitivity was compared between subgroups of premenopausal and postmenopausal women (n = 25 per group) matched for age. Pre- and postmenopausal women were matched to within ± 3.4 years. Because the time since menopause had a skewed distribution (Shapiro-Wilks test; $P < 0.01$), Spearman's rank correlation coefficients were used to investigate the relationship between the time since menopause and insulin-stimulated glucose disposal. All data are expressed as means ± SD, unless otherwise specified.

RESULTS

— Physical characteristics of pre- and postmenopausal women are show in Table 1. Premenopausal women were younger ($P < 0.01$), taller ($P < 0.05$), and

Table 1—*Physical characteristics of premenopausal and postmenopausal women*

Variable	Premenopausal	Postmenopausal
n	43	40
Age (years)	47 ± 3	51 ± 4*
Height (cm)	165 ± 5	162 ± 5†
Weight (kg)	61 ± 8	66 ± 9†
Fat mass (kg)	17 ± 8	23 ± 6*
FFM (kg)	41 ± 4	40 ± 4
Intra-abdominal fat (cm^2)	56 ± 29	88 ± 34*
Subcutaneous abdominal fat (cm^2)	224 ± 112	276 ± 80†

Data are *n* or means ± SEM. *$P < 0.01$; †$P < 0.05$.

weighed less ($P < 0.05$) than postmenopausal women. Differences in body weight were due to a 35% greater ($P < 0.01$) fat mass in postmenopausal women. No difference was found in fat-free tissue mass. Postmenopausal women had greater intra-abdominal ($P < 0.01$) and subcutaneous abdominal fat ($P < 0.05$).

Figure 1 shows differences in insulin-stimulated glucose disposal between pre- and postmenopausal women. Steady-state concentrations for both insulin and glucose were established during the last 30 min of the hyperinsulinemic-euglycemic clamp (data not shown). Insulin levels during the last 30 min of the clamp were similar between pre- (596 ± 165 pmol/l) and postmenopausal groups (609 ± 200 pmol/l) and suppressed endogenous glucose production completely and similarly in both groups (data not shown). No differences were found when glucose disposal was examined on an absolute basis (pre, 436 ± 131 vs. post, 446 ± 120 mg/min), when data were statistically adjusted for FFM (pre, 436 ± 125 vs. post, 445 ± 126 mg/min), or when data were expressed per unit of FFM (pre, 10.7 ± 3.0 vs. 11.5 ± 3.6 mg · kg^{-1} FFM · min^{-1}). In addition, no differences in glucose disposal were noted on an absolute basis (pre, 436 ± 131 vs. post, 451 ± 113 mg/min), after statistical adjustment for FFM via analysis of covariance (pre, 436 ± 125 vs. post, 451 ± 125 mg/min), or per kilogram of FFM (pre, 10.7 ± 3 vs. post, 11.4 ± 3.5 mg · kg^{-1} FFM · min^{-1}; data not shown) when premenopausal women were compared with a subsample (*n* = 30) of postmenopausal women who had not experienced a menses for at least 12 months. Thus, it is unlikely that the inclusion of perimenopausal women in the postmenopausal group affected our ability to examine menopause-related differences in glucose disposal. Insulin-stimulated glucose disposal was also similar between pre- and postmenopausal women after statistical control for age (pre, 422 ± 140 vs. post, 460 ± 139 mg/min) or in a subgroup (*n* = 25 per group) matched for age (pre, 461 ± 121 vs. 463 ± 124 mg/min; data not shown). Moreover, no differences in insulin sensitivity were found when a subsample of premenopausal women, examined during the follicular phase of the menstrual cycle (*n* = 10; age, 47 ± 2 years; insulin sensitivity, 432 ± 84 mg/min), were compared with premenopausal women examined during the luteal phase (*n* = 43, 436 ± 131 mg/min) and postmenopausal women (*n* = 40, 445 ± 126 mg/min).

No relationship was found between time since menopause (months) and insulin-stimulated glucose disposal (mg · kg^{-1} FFM · min^{-1}, $r = -0.03$).

CONCLUSIONS — Our goal was to examine the effect of menopausal status on insulin sensitivity. To accomplish this objective, we measured whole-body insulin-stimulated glucose disposal in middle-aged premenopausal, and early postmenopausal women using the hyperinsulinemic-euglycemic clamp technique. We found no difference in glucose disposal between pre- and postmenopausal women. These results suggest that menopausal status per se does not affect insulin sensitivity.

To our knowledge, only 1 study has directly measured insulin sensitivity in premenopausal and postmenopausal women. Walton et al. (6) used intravenous glucose tolerance tests and minimal model analysis to assess insulin sensitivity in 66 premenopausal and 92 postmenopausal women spanning a wide age range (21–61 years of age). They found no difference in insulin sensitivity between pre- and postmenopausal women, suggesting no effect of the menopause transition on insulin sensitivity. However, because pre- and postmenopausal women differed significantly ($P < 0.01$ for both) in both age (pre, 32 ± 7 vs. post, 52 ± 4 years) and adiposity (i.e., BMI: pre, 21.8 ± 2.4 vs. post, 23.5 ± 2.0 kg/m^2), it is unclear whether the absence of differences in insulin sensitivity between premenopausal and postmenopausal women were due to age, adiposity, or a combination of both. To account for these and other confounding variables, the authors statistically adjusted insulin sensitivity measurements for age, BMI, parity, alcohol consumption, tobacco use, exercise level, and family history of

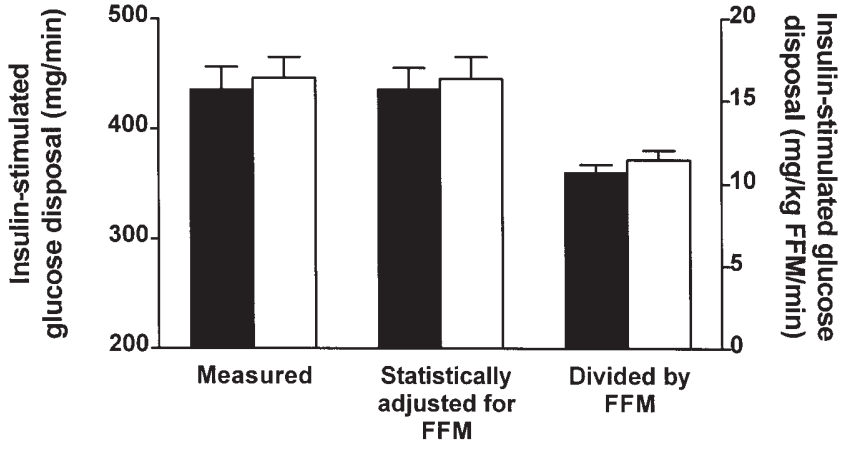

Figure 1—*Differences in insulin sensitivity between premenopausal and postmenopausal women. Closed bars represent premenopausal and open bars postmenopausal women. Both measured values and statistically adjusted values are expressed as mg/min. Statistically adjusted values represent differences after control for FFM by analysis of covariance. Divided by FFM values are expressed as mg · kg^{-1} FFM · min^{-1}. Values are mean ± SEM.*

heart disease and diabetes. After adjustment, insulin sensitivity was 50% greater in postmenopausal compared with premenopausal women. Thus, in contrast to the results of Walton et al. (6) on an unadjusted basis, this finding suggests that the menopause transition is associated with an increase in insulin sensitivity.

For several reasons, the results of Walton et al. (6) deserve further scrutiny. First, despite the fact that postmenopausal women were, on average, older (+20 years) and more obese (+1.7 kg/m^2 BMI) than premenopausal women, no differences in insulin sensitivity were found. In fact, insulin sensitivity was nonsignificantly higher (+9%) in postmenopausal women before statistical adjustment. Both adiposity and age are negative modulators of insulin sensitivity (12–14). Thus, insulin sensitivity would be expected to be lower in postmenopausal women. Second, the finding of increased insulin sensitivity in postmenopausal women is at odds with animal and human studies, which show that ovarian hormone deficiency promotes insulin resistance (2–5). In fact, the authors themselves stated that their results may be due to "....artefacts of the [statistical] adjustment process" (6). Given these caveats, we would suggest that the effect of the menopause transition on insulin sensitivity has yet to be rigorously examined.

In the present study, we controlled for factors that may confound our ability to examine menopause-related differences in insulin sensitivity. First, we compared middle-aged premenopausal and early postmenopausal women (i.e., 21 ± 13 months after the menopause transition) to minimize the confounding effect of age and other factors that change with age on insulin sensitivity. In addition, we examined differences in insulin sensitivity after statistical adjustment for age and in a subgroup of premenopausal and postmenopausal women matched for age (see RESULTS). No menopause-related differences in insulin sensitivity were found after statistical adjustment or matching procedures. Thus, it is unlikely that our comparison of insulin sensitivity between pre- and postmenopausal women was confounded by age. Second, food intake was controlled by providing 3 days of standardized meals before testing, thereby minimizing the possibility that the antecedent diet would affect insulin sensitivity measurements. Third, our selection criteria for pre- and postmenopausal women were standardized to reduce the influence of other confounding variables on insulin sensitivity. We feel that these experimental and analytical considerations lend credibility to our findings.

Insulin sensitivity was measured in premenopausal women during the luteal phase of the menstrual cycle. This could confound the comparison of insulin sensitivity with postmenopausal women if menstrual cycle phase affects insulin-stimulated glucose disposal. However, those studies that have examined insulin-stimulated glucose disposal during different menstrual cycle phases using the hyperinsulinemic-euglycemic clamp have found no effect (15,16). In a recent study, Godsland (17) concluded that insulin sensitivity, as measured by hyperinsulinemic-euglycemic clamps, is not affected by menstrual cycle phase. Furthermore, differences in insulin sensitivity between menstrual cycle phases observed in those studies using other techniques, such as the intravenous glucose tolerance test, were primarily due to decreased glucose-induced glucose disposal (18). Because glucose levels are not elevated during the hyperinsulinemic-euglycemic clamp, the mass effect of glucose on its own disposal is not included in the insulin sensitivity measurement. In addition, we found no difference in insulin sensitivity between premenopausal women studied during the follicular phase of the cycle and postmenopausal women (see RESULTS). Thus, we do not believe that the timing of our insulin sensitivity measurement affected our ability to detect menopause-related differences in insulin sensitivity, as measured by the hyperinsulinemic-euglycemic clamp.

Despite similar selection criteria for degree of adiposity (i.e., BMI ≤30 kg/m^2), postmenopausal women had greater total body, subcutaneous abdominal, and intra-abdominal fat compared with premenopausal women. These results are in accordance with several cross-sectional and longitudinal studies that show an increase in total and central adiposity with the menopause transition (9,19). Unfortunately, these differences in adiposity complicate the interpretation of our results, because increased total and abdominal adiposity are associated with reduced insulin sensitivity (13,20). For example, one plausible conclusion from our findings might be that postmenopausal women are more insulin sensitive than premenopausal women because insulin-stimulated glucose disposal rates were similar between groups, despite the greater total and abdominal adiposity in postmenopausal women. In fact, when glucose disposal is adjusted for both FFM and intra-abdominal fat using analysis of covariance, glucose disposal is higher (P = 0.01) in postmenopausal women (478 ± 118 mg/min) than that in premenopausal women (pre, 405 ± 118 mg/min). Although it is possible to conclude from this finding that the menopause transition increases insulin sensitivity, closer consideration of the statistical adjustment procedure brings this conclusion into question. Specifically, if the statistical relationship between glucose disposal and intra-abdominal fat does not accurately reflect the underlying physiological association between these variables, the analysis of covariance–derived adjusted glucose disposal values may be erroneous: We believe this to be the case. To support our position, we consider both the method of statistical adjustment and the physiological relationship of intra-abdominal fat to insulin-stimulated glucose disposal.

Analysis of covariance adjusts group mean insulin-stimulated glucose disposal values for the linear relationship between glucose disposal and the covariate B intra-abdominal fat, for example. Specifically, the slope of the relationship of glucose disposal to intra-abdominal fat is used together with mean values for glucose disposal and intra-abdominal fat to derive group-adjusted glucose disposal values (analysis of covariance procedures were described previously [21]). The slope of the relationship between glucose disposal and intra-abdominal fat in our sample (n = 83) was −1.462 (mg/min)/cm^2. Thus, a reduction in glucose disposal of 1.462 mg/min is expected to occur for every 1 cm^2 increase in intra-abdominal fat. This slope is a mathematical or statistical description of the linear relationship between glucose disposal and intra-abdominal fat. However, whether this slope reflects the true physiological association between insulin-stimulated glucose disposal and intra-abdominal fat is not clear.

A recent study by Goodpaster et al. (22) provides data from which to evaluate the physiological relationship between insulin-stimulated glucose disposal and intra-abdominal fat. In this study, 32 obese sedentary men and women underwent a 4-month weight loss program. In women, glucose disposal increased by 39 mg/min and intra-abdominal fat decreased by 44 cm^2. Moreover, the weight loss–induced reduction in intra-abdominal fat was found

to explain 15% of the increase in glucose disposal. Although the slope of the relationship between the change in glucose disposal and the change in intra-abdominal fat was not provided in the manuscript, sufficient data are available to allow its estimation. If 15% of the improvement in glucose disposal, or 6 mg/min (39 mg/min, 15% = 6 mg/min), is due to the reduction in intra-abdominal fat, the slope of the relationship between glucose disposal and intra-abdominal fat would be 0.136 (mg/min)/cm^2 (i.e., 6 mg/min) −44 cm^2 = −0.136 (mg/min)/cm^2). This calculated slope should approximate the actual physiological relationship between the changes in glucose disposal and intra-abdominal fat because, by definition, the slope is equivalent to the change in glucose disposal relative to the change in intra-abdominal fat. Thus, it appears as if the effect of intra-abdominal fat on glucose disposal derived from our cross-sectional study using statistical analysis represents a 10-fold overestimation of the physiological association between these variables (slope = −1.462 [mg/min]/cm^2 for statistical analysis vs. −0.136 [mg/min]/cm^2 from physiological studies). If we use the slope of the relationship between glucose disposal and intra-abdominal fat derived from the data of Goodpaster et al. (22), the 32 cm^2 greater intra-abdominal fat area in postmenopausal women in the present study would be expected to account for only a 4.4 mg/min lower glucose disposal rate (i.e., 32 cm^2 * −0.136 (mg/min)/cm^2 = −4.4 mg/min). These results underscore the need for caution in the interpretation of statistical analyses when available physiological data suggest an alternative conclusion. Thus, from a physiological perspective, we believe it is unlikely that menopause-related differences in intra-abdominal fat, noted in the present study, would significantly affect insulin sensitivity.

Another interpretation of our findings should be considered. The menopause transition may be associated with a reduction in insulin sensitivity, but postmenopausal women were evaluated too early in the postmenopausal state (21 ± 13 months) to observe these changes. It is our working hypothesis that the menopause transition is associated with alterations in energy balance (2) and intra-abdominal fat cell metabolism (23) that predispose postmenopausal women to the accumulation of body fat with preferential storage in the intra-abdominal depot. The accumulation of total and intra-abdominal fat, in turn, reduces insulin sensitivity. Evidence from our laboratory (2) and others (19) provide evidence to support the first 2 steps in this hypothetical pathway. Moreover, both of these changes appear to take place in relatively close proximity to the menopause transition. However, the final step, adiposity-related reductions in insulin sensitivity, may take longer to develop. Although we found no relationship between insulin sensitivity and time since menopause, it may be necessary to examine women who are further removed (>2 years) from the menopause transition to detect significant differences in insulin sensitivity.

In conclusion, our data suggest that postmenopausal status is not associated with decreased insulin sensitivity, as assessed by the hyperinsulinemic-euglycemic clamp. Although this conclusion is at odds with the 1 study that has evaluated the effect of menopausal status on insulin sensitivity in humans (6) and studies in ovariectomized rats (4,5), our findings are supported by studies in nonhuman primates that show no effect of ovariectomy on insulin sensitivity (24). However, we cannot discount the fact that menopause alters other aspects of glucose metabolism not measured by the hyperinsulinemic-euglycemic clamp (e.g., glucose-induced glucose disposal). Moreover, the possibility that the absence of menopause-related differences in insulin sensitivity was due to the cross-sectional design of our study cannot be dismissed. Thus, longitudinal studies that examine changes in insulin sensitivity as women transition from the premenopausal to the postmenopausal state are needed to clarify our results.

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